ELSEVIER

Atherosclerosis Supplements 14 (2013) 93–99

ATHEROSCLEROSIS SUPPLEMENTS

www.elsevier.com/locate/atherosclerosis

Effect of specific lipoprotein(a) apheresis on coronary atherosclerosis regression assessed by quantitative coronary angiography

Maya S. Safarova [a], Marat V. Ezhov [a], Olga I. Afanasieva [a], Yuriy G. Matchin [a], Ruslan V. Atanesyan [a], Irina Yu. Adamova [a], Elena A. Utkina [a], Gennadiy A. Konovalov [b], Sergei N. Pokrovsky [a,*]

[a] *Cardiology Research Center 15A, 3rd Cherepkovskaya Street, 121552 Moscow, Russia*
[b] *MEDSI Clinic 3A, Georgian Lane, 123056 Moscow, Russia*

Abstract

Aim: To evaluate the effect of specific lipoprotein(a) [Lp(a)] apheresis on coronary atherosclerosis progression in coronary heart disease (CHD) patients with elevated Lp(a) levels.
Methods: A total of 30 subjects (mean age 53.5 ± 8.3 years, 70% male) with CHD verified by angiography, Lp(a) > 50 mg/dL, and low density lipoprotein cholesterol (LDL-C) ≤ 2.5 mmol/L on chronic statin treatment were prospectively evaluated for 18 months. Patients were allocated to receive specific Lp(a) apheresis, which was carried out weekly with Lp(a) Lipopak® columns (POCARD Ltd., Russia) ($n = 15$), or atorvastatin only ($n = 15$). Blinded quantitative coronary angiography analyses of percent diameter stenosis and minimal lumen diameter (MLD) were performed at baseline and after the 18-month treatment period.
Results: By the single specific Lp(a) apheresis procedure, Lp(a) level decreased by an average of 73 ± 12% to a mean of 29 ± 16 mg/dL, and mean Lp(a)-corrected LDL-C decreased by 7% to a mean of 1.4 mmol/L. Median percent diameter stenosis was reduced by −2.0 (95% confidence interval [CI], −5.0–0.0) with apheresis ($p < 0.01$ in comparison with baseline), and increased by 3.5 (0.0–6.9) with atorvastatin ($p < 0.001$ between the groups). The effect on MLD was more favorable with apheresis than with atorvastatin: 0.20 ± 0.39 mm, as compared with 0.01 ± 0.34 mm, $p = 0.04$. Lp(a) apheresis had greater efficacy regarding the amount of regressed/stabilized coronary segments than atorvastatin alone in the majority of patients (chi-square test 13.61, $p < 0.005$).
Conclusion: Specific Lp(a) apheresis for 18 months produced coronary atherosclerosis regression in stable CHD patients with high Lp(a) levels and reached LDL-C goals.

Keywords: Lipoprotein(a); Lp(a) apheresis; Coronary atherosclerosis; Regression; Angiography; Plaque

1. Introduction

Although it has been known for 50 years, lipoprotein(a) [Lp(a)] has finally been acknowledged as an independent cardiovascular risk factor [1]. It was clearly demonstrated in the series of experimental, epidemiological, and genetic studies that this apolipoprotein B100-S–S-apo(a)-containing particle with atherothrombogenic properties is directly associated with coronary disease. But available therapeutic approaches are quite limited in this field, especially in patients with extremely high Lp(a) levels. No intervention trials have shown the causality of this relation, and no recommendations for Lp(a) reduction could be found in current guidelines. Studies of the effect of statins on Lp(a)

* Corresponding author. Tel.: +7 495 414 6732, +7 495 729 8223 (mobile); fax: +7 495 414 6820.
E-mail addresses: Dr.Safarova@gmail.com (M.S. Safarova), Marat_Ezhov@mail.ru (M.V. Ezhov), Afanasolg@yandex.ru (O.I. Afanasieva), Konovalov@medsi.ru (G.A. Konovalov), Dr.Pokrovsky@mail.ru (S.N. Pokrovsky).

1567-5688/$ - see front matter © 2012 Elsevier Ireland Ltd. All rights reserved.
http://dx.doi.org/10.1016/j.atherosclerosissup.2012.10.015

levels show contradictory results at best, including reports of both decreases and increases of Lp(a) levels upon statin therapy. Nonetheless, it has been reported that statin therapy does prevent Lp(a) atherogenicity, with no documentation of this phenomena *in vivo*. Since 1981 several original systems for extracorporeal low density lipoprotein (LDL) elimination, called lipoprotein apheresis, have been designed. Comparisons of these systems were made in several reviews [2–4]. It should be mentioned that due to the close structural resemblance between LDL and Lp(a) particles, lipoprotein apheresis removes both lipoprotein classes from the blood. However, the number of Lp(a) particles in human plasma is significantly less than it is for LDL, even in cases with extremely elevated Lp(a) levels. With regard to Lp(a), technologies designed for removal of LDL are less selective for Lp(a), and eliminate Lp(a) from the blood on the basis of LDL/Lp(a) ratio. Specific Lp(a) apheresis is the only possible method that solely targets Lp(a) [5]. The usefulness, safety and efficacy of Lp(a) apheresis have been already shown in a clinical setting, representing a more specific potential than lipoprotein apheresis regarding Lp(a). This approach allows the most efficient elimination of the particle with a decrease of at least 88% of the pre-treatment Lp(a) level [6,7]. Later our columns were used in the UK [8], and in Germany for specific Lp(a) apheresis [9–12]. However the indication for the treatment of patients with Lp(a) excess is still under debate. Based on the hypothesis that Lp(a) excess has a detrimental role in atherogenesis, we evaluated the efficacy of specific Lp(a) apheresis on coronary atherosclerosis burden in patients with CHD on the background of optimal medical treatment.

2. Methods

2.1. Study design and population

This prospective, open-label, parallel-group, partially blinded clinical trial was performed at two centers: Cardiology Research Center, a federal state institution of the Ministry of Health, and MEDSI clinic, a private care hospital, both located in Moscow, Russia. The protocol was approved by the Institutional Ethics Committee, and written informed consent was obtained from all patients. Between September, 2009, and October, 2010, we enrolled men and women $\geq$18 years of age with stable CHD requiring a clinically indicated coronary angiography. Inclusion required at least one documented stenosis of $\geq$50% angiographic luminal diameter narrowing by visual estimation in any coronary vessel. All participants had an Lp(a) level of more than 50 mg/dL, and an LDL-C of less than 2.5 mmol/L on a statin therapy for more than one month before the enrollment. Patients were excluded if they had experienced: acute coronary syndromes within the prior three months; familial hypercholesterolemia; triglycerides (TG) $>$ 4.5 mmol/L; uncontrolled diabetes; hypertension; or heart failure; had renal or thyroid dysfunction; liver disease; or current treatment with other than statins lipid-lowering drugs. Individuals who needed urgent myocardial revascularization were not included. After a run-in period with open-label atorvastatin, a total of 30 eligible subjects were divided with an allocation ratio of 1:1 into two main groups for the treatment during 18 months which was followed by a second angiography. In the active group patients received apheresis procedures weekly with specific for Lp(a) immunosorbent columns. Patients from both groups received standard medical therapy in accordance with the recommendations for secondary prevention of CHD [13]. Basic lipid-lowering medication consisted of atorvastatin. There were no protocol-directed changes in medication; dose of atorvastatin could be titrated with the variation in LDL-C concentration $<$1.0 mmol/L for the whole study period from the initial visit.

2.2. Lp(a) apheresis

Lp(a) apheresis procedures were carried out weekly with Lp(a) Lipopak® columns (POCARD Ltd., Russia) according to the standard protocol [7,14]. Patients were connected via cubital venous catheter with a centrifuged type plasmaseparator (COBE® Spectra system, USA); plasma was then passed through immunoadsorption columns with sheep polyclonal monospecific antibodies against human apolipoprotein(a). For each patient, we used a pair of 200 mL columns, designed for personal multiple use. The total duration of a procedure was approximately 3 h in which 3–5 chromatography cycles were run in order to treat 5.5 $\pm$ 1.0 L of plasma. Anticoagulation was performed with unfractionated heparin.

2.3. Quantitative coronary angiography

All patients underwent selective coronary angiography according to a defined protocol as part of the entry criteria for patients to be enrolled in the study, and follow-up angiography was performed at the end of the study. After administration of intracoronary nitroglycerin (250 μg), standard angiographic images were obtained with the Philips Allura Xper FD10 cardiovascular X-ray system and recorded on a DICOM-formatted CD. During the baseline angiogram, the sequence of projections, the degree of axial rotation, the degree of cranial/caudal angulation, the type and size of catheter used were documented. A single operator performed all angiographic examinations. All films were read in one angiographic laboratory by two observers who were unaware of the treatment assignments. Measurements were performed at the end of the study, after both baseline and follow-up examinations were available. For the evaluation, the researchers used an American Heart Association 15-segment model [15] to score a coronary artery tree. Angiographic analysis neglected coronary segments with diameters smaller than 2 mm. Segments that

included a lesion that had undergone angioplasty, side branches arising from a stented coronary segment, and coronary bypass grafts were excluded from the analysis. Computer assisted quantitative analysis was performed using end-diastolic frames with the Xcelera 105122 workstation (PHILIPS Medical Systems, The Netherlands). The reference diameter and the most severe site of atherosclerosis in the segment, (the minimal lumen diameter, MLD) were measured in each segment. Percent stenosis was calculated from the narrowest lesion in each segment: [(reference diameter − MLD)/reference diameter] × 100. Clinically relevant regression or progression was defined as a change from baseline to follow-up of ≥10% for percent diameter stenosis [16] and ≥0.2 mm for MLD [17].

2.4. Biochemical assessments

During treatment, levels of total cholesterol (TC), triglycerides (TG), high density lipoprotein cholesterol (HDL-C), LDL-C, and Lp(a) were measured at 1, 9, and 18 months. The Lp(a) concentration was measured by ELISA with monospecific sheep polyclonal antibody against human Lp(a) as previously described [7]. The method was validated with respect to two commercial kits "TintElize™ Lp(a)" (Biopool AB Sweden) and "Immunozym Lp(a)" (Progen Biotechnik GmbH, Germany). The control materials "Technoclone" Austria, approved by IFCC, were used to standardize the ELISA.

Since all included patients had high Lp(a) levels, to avoid overestimation of LDL cholesterol fraction estimated LDL-C levels were corrected for cholesterol derived from Lp(a), usually around 30% of Lp(a) mass. Corrected LDL-C (LDL-C_{corr}) was estimated using Dahlen's modification of the Friedewald formula [18].

For values in mg/dL:

$$\text{LDL-C}_{corr} = \text{TC} - (\text{HDL-C}) - (\text{TG}/5) - [\text{Lp(a)}(\text{mg/dL}) \times 0.3].$$

For values in mmol/L:

$$\text{LDL-C}_{corr} = \text{TC} - (\text{HDL-C}) - (\text{TG}/2.2) - [\text{Lp(a)}(\text{mg/L}) \times 0.3/386.7].$$

2.5. Statistical analysis and study end-points

For continuous variables with an approximately normal distribution, means ± standard deviation (SD) are reported. For parameters with non-Gaussian distribution data are expressed as median and interquartile ranges. In univariate analysis, continuous variables were compared by two-sided *t*-tests and Wilcoxon signed-rank test. Fourfold tables were analyzed by two-sided Fisher exact test or Yates corrected χ^2 test. For contingency 2 × 3 tables, χ^2 test was used. The proportion of patients categorized as regressors versus progressors was tested using a 2-sided binomial test. The *p* values for all tests were two-tailed, and differences were considered to be significant at the 0.05 level. An independent investigator double-checked all measurement calculations and database entries. All statistical analyses were performed with SPSS software (version 16).

The predefined primary end-point was the absolute change from baseline in mean percent diameter stenosis, determined by quantitative coronary angiography (QCA) data after 18 months. The secondary angiographic end-point was the absolute change in mean MLD in the same coronary segments. Spearman's rank sum analysis was applied to seek correlation between lipid changes and study end-points.

3. Results

3.1. Characteristics of the patients

From baseline data we identified 122 consecutive subjects: 51 patients were excluded because lipid inclusion criteria were not met, nine were on a combined lipid-lowering therapy, 28 declined to participate and four had poor peripheral venous access for the performance of regular apheresis. After 18 months of treatment, 30 patients completed the study and underwent repeat QCA. Baseline characteristics were comparable between two treatment groups with regard to age, sex, cardiovascular risk factors, and clinical presentation (all patients had stable angina by study design). Baseline medication use and laboratory values did not differ significantly between study participants (Table 1).

3.2. Biochemical measurements

In both treatment groups lipid values were adequately controlled during the active study period. The baseline and on-treatment lipid parameters are shown in Fig. 1. After a run-in period, the level of TC was 4.5 ± 0.5 mmol/L; LDL-C, 2.3 ± 0.3 mmol/L; HDL-C, 1.3 ± 0.3 mmol/L; TG, 1.4 ± 0.5 mmol/L, Lp(a), 105 ± 37 mg/dL, and corrected LDL-C, 1.8 ± 0.7 mmol/L. Acute effects of specific Lp(a) apheresis treatment (difference before and immediately after procedure) resulted in a 73% reduction in Lp(a), producing a final mean of 29 ± 16 mg/dL; LDL-C decreased by 17% to a mean of 1.4 mmol/L, corrected LDL-C decreased by 7% to a mean of 1.4 mmol/L. The final change in Lp(a) level in the apheresis group was −31.7 ± 22.3 mg/dL, as compared with 4.8 ± 10.8 mg/dL in the atorvastatin monotherapy group ($p = 0.0001$). The final change in LDL-C level in the apheresis group was −0.1 ± 0.4 mmol/L, as compared with −0.1 ± 0.3 mmol/L in the atorvastatin only group ($p = 0.96$). The same results were obtained for LDL-C_{corr} level (mmol/L): −0.2 ± 0.6 and −0.1 ± 0.6 for apheresis and control groups, respectively ($p = 0.65$). The changes of the mean in-treatment HDL-C and TG values from those at baseline were also stable through the treatment period.

Table 1
Baseline characteristics of patients who completed the 18-month primary end-point assessment, according to treatment group.

Variable, *n*(%)	Lp(a) apheresis ($N = 15$)	Atorvastatin ($N = 15$)	*p* Value
Age, years	51.4 ± 9.3	55.6 ± 6.8	0.17
Male sex	11 (73)	10 (67)	1.0
Body-mass index	27.5 ± 4.0	28.3 ± 7.3	0.72
Body-mass index > 30	4 (27)	3 (20)	1.0
Hypertension	9 (60)	9 (60)	1.0
Current smoking	4 (27)	3 (20)	1.0
Diabetes mellitus	3 (20)	1 (7)	0.60
Family history of coronary heart disease	7 (47)	8 (53)	1.0
History of coronary heart disease			
Angina pectoris III–IV class	7 (47)	4 (27)	0.45
Myocardial infarction	12 (80)	10 (67)	0.68
Percutaneous coronary revascularization	11 (73)	8 (53)	0.45
Coronary bypass surgery	1 (7)	1 (7)	1.0
Mean atorvastatin dose, mg	34 ± 13	32 ± 10	0.69
Concomitant medications			
Antiplatelets	15 (100)	15 (100)	1.0
Beta-blockers	13 (87)	12 (80)	1.0
Angiotensin-converting enzyme inhibitors	6 (40)	10 (67)	0.27
Angiotensin receptor antagonists	7 (47)	2 (13)	0.11
Calcium antagonists	5 (33)	6 (40)	1.0
Organic nitrates	7 (47)	6 (40)	1.0
Biochemical values			
Lipoprotein(a), mg/dL	103 ± 23	101 ± 52	0.88
TC, mmol/L	4.6 ± 0.5	4.5 ± 0.5	0.41
LDL-C, mmol/L	2.2 ± 0.2	2.3 ± 0.3	0.38
LDL-C_{corr}, mmol/L	2.0 ± 0.6	1.9 ± 0.4	0.60
HDL-C, mmol/L	1.2 ± 0.3	1.4 ± 0.3	0.06
Triglycerides, mmol/L	1.4 ± 0.5	1.4 ± 0.5	0.85

Plus–minus values are means ± SD. The body-mass index is the weight in kilograms divided by the square of the height in meters. To convert the values for lipoprotein(a) to mmol/L multiply by 0.0357. To convert the values for cholesterol to mg/dL, divide by 0.0259. To convert the values for triglycerides to mg/dL, divide by 0.0113. LDL denotes low density lipoprotein, and HDL high density lipoprotein.

3.3. Efficacy end-points

The baseline and 18-month post-therapy angiographic end-points are summarized in Table 2.

A total of 92 coronary segments in the 30 patients (median, 3 segments per patient) had valid stenosis and MLD measurements at both baseline and the end of the study. Specific Lp(a) apheresis showed greater efficacy to standard medical treatment regarding the change in the mean percent diameter stenosis at 18 months. Primary efficacy end-point decreased by 5.05 ± 12.38% in the Lp(a) intervention group and increased by 5.04 ± 11.43% in the control group ($p < 0.01$ for the change from baseline in each group; $p < 0.001$ for the between-group comparison). For the secondary efficacy end-point, the effect was also more favorable with Lp(a) apheresis than with the control group taking atorvastatin monotherapy. Apheresis regimen caused a significant increase in the mean MLD by up to 14% ($p = 0.006$) versus lack of changes in the drug-only group ($p = 0.62$).

The apheresis regimen showed superior efficacy to atorvastatin monotherapy regarding the number of regressed coronary segments: in 43% of the analyzed segments we revealed regression and only 14% progressed, whereas with atorvastatin 50% showed progression and only 20% regressed. Changes of <10% from baseline were seen in 18 (43%) segments on Lp(a) apheresis, and in 15 (30%) lesions from atorvastatin group ($N = 92$, chi-square test 13.61, $p < 0.005$). Most apheresis-treated patients showed a reduction in the percent diameter stenosis, as compared with drug-regimen group (60% versus 20% with atorvastatin, $p = 0.06$).

By step-wise multiple regression analysis, among evaluated lipids and lipoproteins, only the percentage change in Lp(a) on follow-up was positively correlated with the primary efficacy end-point ($r = 0.270$, $p < 0.05$). Furthermore, lower 18-month post-therapy levels of Lp(a) were associated with greater regression for percent diameter stenosis, independently from LDL levels ($r = 0.33$, $p < 0.05$).

4. Discussion

Data from *in vitro* and animal studies implicate the dual structure of Lp(a) in both atherosclerosis, including accumulation of Lp(a) in atherosclerotic plaques, and promotion of thrombosis by inactivating the tissue factor pathway inhibitor. Experimental studies indicate that Lp(a) is transferred into the intima by a mechanism similar to that of LDL [19], and it is thought that if LDL treatment goals are achieved the atherogenic effects of Lp(a) are negated [20]. However, this hypothesis has never been verified in the setting of a clinical interventional trial. Evidence from epidemiological trials and meta-analysis demonstrates independent and continuous association between high Lp(a) levels and risk of CHD. According to the European consensus statement, in patients at high to moderate risk of cardiovascular disease Lp(a) level should be reduced under 50 mg/dL as a secondary priority after reduction in LDL [1]. Lp(a) levels are generally not influenced by lifestyle and to date no widely useable pharmacologic method for lowering Lp(a) is available. At present, only niacin at high doses and several investigational lipid-lowering agents have shown to lower Lp(a). From the available regimens, lipoprotein apheresis is the most effective method in reducing this particle. Specifically, Jaeger BR et al. clearly demonstrated that in patients with CHD and high Lp(a) levels apheresis treatment can significantly reduce coronary risk primarily due to prominent decrease in Lp(a) levels [21]. However, listed therapies are not selective for Lp(a) and also favorably influence levels of TC, TG, very low density (VLDL-C), LDL and HDL cholesterol. Comparison of different systems for lipoprotein apheresis for the treatment

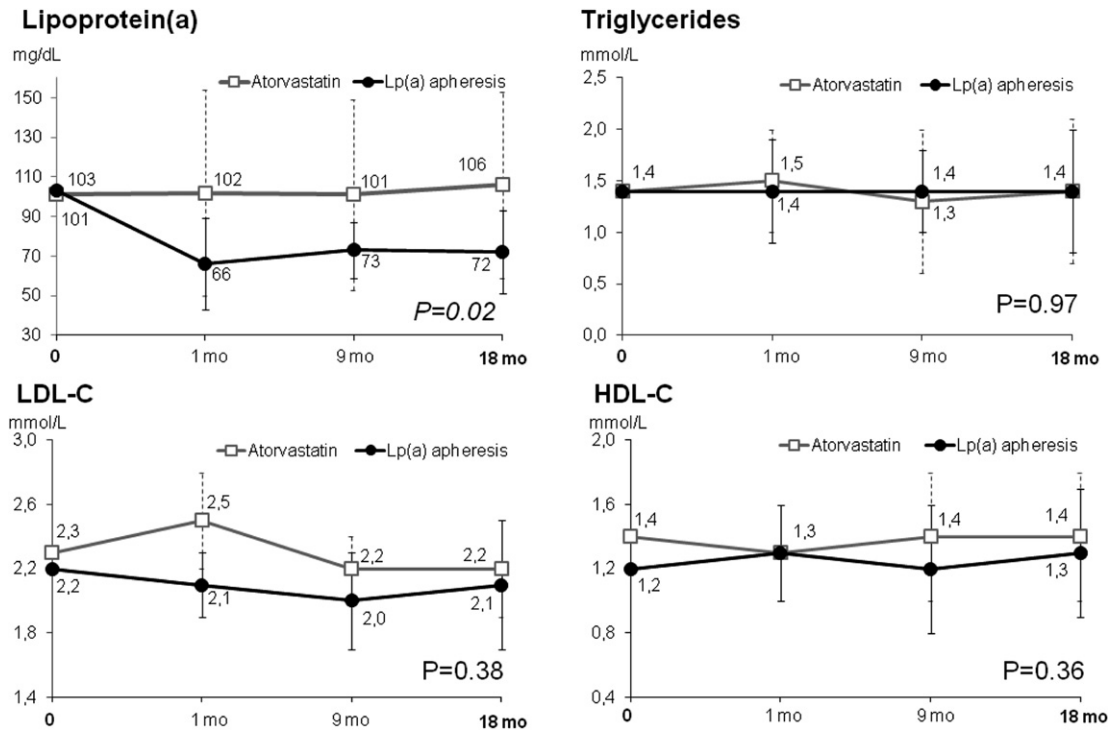

Fig. 1. Mean changes in lipid and lipoprotein levels over the 18-month study period, according to treatment group. The p values are given for the comparison between the two treatment groups at 18 months. The vertical bars indicate the standard deviation. HDL-C denotes high density lipoprotein cholesterol, and LDL-C low density lipoprotein cholesterol.

of CHD patients with elevated Lp(a) was recently done by C. Keller [22] and H. Borberg [23]. Since specific against human Lp(a) immunosorbent columns were designed by our group in 1991 [5], the effectiveness and safety of the method were proven in clinical practice by different groups [6–12,14,24]. With regard to other LDL apheresis technologies, Lp(a) Lipopak® system provides highly specific efficacious reduction in Lp(a) levels.

This proof of concept imaging study compared the effect of weekly specific Lp(a) apheresis with standard medical approach on coronary disease progression. As an acute effect, Lp(a) apheresis reduced Lp(a) to a mean of 30 mg/dL which is currently considered an appropriate target level [1]. In both regimens, mean values of LDL-C reached recommended goals less than 2.6 mmol/L during the whole study period. An apparent lack of significant change in LDL-C level was explained by the fact that all patients were already on the chronic statin treatment, and other lipid-lowering medications were prohibited. Concentration of HDL also achieved the desired level for secondary prevention of 1.3 mmol/L (50 mg/dL).

For the cases with elevated Lp(a) $>$ 50 mg/dL, to avoid mistakes in correct LDL-C estimation, it was necessary to calculate LDL-C_{corr}. For example, in a patient with Lp(a) level of 60 mg/dL and LDL-C level of 2.7 mmol/L, LDL-C_{corr} would be 2.2 mmol/L. This position also explains difficulties in reaching recommended LDL-C target with standard statin dosage in this group of patients. Further studies are needed to evaluate the influence of novel lipid treatment goals on the prognosis of patients with Lp(a) excess.

Comparing the two treatment strategies, the progression rate was significantly lower in the apheresis group. The change in atherosclerosis burden was negative in the Lp(a) immunoadsorption group (a difference of −5% compared with baseline), showing a disease regression, as assessed by quantitative coronary angiography ($p = 0.01$). In this selected population of CHD patients with extremely high Lp(a) levels we observed a significant net progression of coronary atherosclerosis in drug-regimen only group ($p = 0.003$). As compared with the atorvastatin regimen, Lp(a) apheresis led to a prominent increase in the mean MLD by 0.20 ± 0.40 mm (median, 0.17 mm). Significant differences favoring intensive Lp(a) lowering were observed regarding the proportion of coronary segments categorized as regressed versus progressed ($p = 0.02$). The present study adds the argument that Lp(a) maintains its proatherogenic properties, even if the level of LDL-C is below 2.5 mmol/L.

Which strategies should be used to maximize the therapeutic benefit of patients with elevated Lp(a) levels remains somewhat controversial. The most promising finding of the 1.5 years of regular Lp(a) apheresis is the possibility to reverse coronary atherosclerosis, as evidenced by the fact that four-fifths of patients with Lp(a) excess and achieved mean LDL-C level of 2.2 mmol/L with atorvastatin had disease progression versus two fifths of patients with mean LDL-C of 2.1 mmol/L in Lp(a) apheresis group ($p = 0.06$).

Table 2
Results of 18-months treatment of Lp(a) apheresis and control groups by quantitative angiographic analysis, according to treatment group.

QCA parameters	Lp(a) apheresis	Atorvastatin	*p* Value
Number of coronary segments	42 segments	50 segments	
Percent diameter stenosis, %			
Baseline			
Mean	44.31 ± 15.95	43.68 ± 13.46	0.95
Median (95% CI)	40.00 (37.29–47.00)	43.50 (39.86–47.51)	
18-month			
Mean	39.26 ± 13.61	48.72 ± 14.77	0.001
Median (95% CI)	36.50 (32.00–43.35)	49.00 (40.07–52.93)	
Mean change from baseline	−5.05 ± 12.38	5.04 ± 11.43	0.0004
Median change from baseline	−2.00 (−5.00–0.00)	3.50 (0.00–6.93)	
Number with regression, *n* (%)	18 (43)	10 (20)	0.02*
Minimal lumen diameter, mm			
Baseline			
Mean	1.39 ± 0.63	1.44 ± 0.50	0.52
Median (95% CI)	1.30 (0.99–1.63)	1.40 (1.17–1.64)	
18-month			
Mean	1.59 ± 0.54	1.45 ± 0.65	0.08
Median (95% CI)	1.56 (1.34–1.73)	1.26 (1.16–1.58)	
Mean change from baseline	0.20 ± 0.39	0.01 ± 0.34	0.04
Median change from baseline	0.17 (0.03–0.36)	0.05 (−0.05–0.17)	

Plus–minus values are means ± SD. CI denotes confidence interval. The *p* value for the between-group comparison of the change from baseline was calculated with the use of Wilcoxon signed-rank test. *Fisher's exact test.

Positive effect of LDL centric treatment is well established and our data reinforce the clinical usefulness of Lp(a) intervention. We postulate that in patients with established CHD who have optimally controlled LDL-C on a statin, those who have residually higher levels of Lp(a) have a clinical benefit from co-administration of Lp(a) apheresis.

Several limitations in our study should be noted. First, an open-label design was imposed by complexity to form a control group receiving apheresis treatment with sham-columns. We compensated for the lack of placebo group by blinding observers to the treatment assignments. Second, the study was not powered to evaluate differences in major adverse cardiovascular events. These outcomes were recorded, but were not included in the present analysis. Third, relatively small sample size does not allow application of our findings to secondary prevention in broader community. The trial involved patients undergoing clinically indicated coronary angiography with extreme Lp(a) levels. The next logical step would be a large scale, randomized trial on Lp(a) guided strategy to address this issue.

5. Conclusions

For the first time in the clinical trial treatment of CHD patients with elevated Lp(a) levels undergoing specific Lp(a) apheresis for 18 months produced regression of coronary atherosclerosis by decreasing percent diameter stenosis and improving minimal lumen diameter. Positive results of this study provide the evidence in using Lp(a) as a therapeutic target for achieving a beneficial effect on atherosclerotic disease burden on the top of optimal medical treatment.

Conflict of interest statement

All authors report no financial relationships or conflicts of interest regarding the content herein.

Acknowledgments

The preliminary data of this study were presented at the 80th European Atherosclerosis Society Congress. Authors thank all the investigators and staff of the *Moscow apheresis study* for their valuable contribution, and all the patients who agreed to participate in this trial. We appreciate the dedicated help of the colleagues and nurses from the MEDSI clinic, where the apheresis procedures were run for their help and contribution in this study. The study was supported by the research grant No 8/3-284n-10 from the Moscow State Government.

References

[1] Nordestgaard BG, Chapman MJ, Ray K, et al. Lipoprotein(a) as a cardiovascular risk factor: current status. Eur Heart J 2010;31:2844–53.
[2] Thompson G. LDL apheresis. Atherosclerosis 2003;167(1):1–13.
[3] Thompson G. Heart-UK LDL apheresis working group. Recommendations for the use of LDL apheresis. Atherosclerosis 2008;198(2):247–55.
[4] Bambauer R, Bambauer C, Lehmann B, Latza R, Schiel R. LDL-apheresis: technical and clinical aspects. Scientific World Journal 2012;2012:19. Article ID 314283.
[5] Pokrovsky SN, Adamova IY, Afanasieva OI, Benevolenskaya GF. Immunosorbent for selective removal of lipoprotein(a) from human plasma: in vitro study. Artif Organs 1991;15:136–40.
[6] Susekov AV, Afanaséva OI, Adamova IIu, Liakishev AA, Kukharchuk VV, Pokrovskiĭ SN. Use of immunosorption for selective decrease of lipoprotein(a) levels in patients with coronary atherosclerosis. Kardiologiia 1992;32(11–12):52–6.
[7] Pokrovsky SN, Sussekov AV, Afanasieva OI, et al. Extracorporeal immunoadsorption for the specific removal of lipoprotein(a) (Lp(a) apheresis): preliminary clinical data. Chem Phys Lipids 1994;67/68:323–30.
[8] Thompson G, Sussekov A. Radical therapy of atherosclerosis by apheresis or liver transplantation. In: Woodford F, Davignon J,

Sniderman A, editors. Atherosclerosis X. Amsterdam: Elsevier Science; 1995. p. 549–52.

[9] Ullrich H, Lackner K, Schmitz G. Lipoprotein(a)-apheresis in the secondary prevention of coronary heart disease. Transfus Sci 1996; 17:511–7.

[10] Bambauer R, Schiel R, Keller HE, Klinkmann J, Latza R. Low-density lipoprotein apheresis in the treatment of two patients with coronary heart disease and extremely elevated lipoprotein(a) levels. Artif Organs 1996;20:340–3.

[11] Ullrich H, Lackner KJ, Schmitz G. Lipoprotein(a) apheresis in severe coronary heart disease: an immunoadsorption method. Artif Organs 1998;22:135–9.

[12] Straube R, Kingreen H. Lipoprotein(a) immunapheresis in the treatment of familial lipoprotein(a) hyperlipoproteinemia in a patient with coronary heart disease. Ther Apher 1998;2:243–5.

[13] Smith Jr SC, Allen J, Blair SN, et al. AHA/ACC guidelines for secondary prevention for patients with coronary and other atherosclerotic vascular disease: 2006 update. Circulation 2006;113: 2363–72.

[14] Pokrovsky S, Afanasieva O, Adamova I, et al. Lipoprotein(a) extracorporeal elimination by specific immunoadsorption for the treatment of CHD patients. Atherosclerosis 2000;151(1):249.

[15] Dodge JT, Brown BG, Bolson EL, et al. Intrathoracic spatial location of coronary segments on the normal human heart. Circulation 1988; 78:1167–80.

[16] Brown G, Albers JJ, Fisher LD, et al. Regression of coronary artery disease as a result of intensive lipid-lowering therapy in men with high levels of apolipoprotein B. N Engl J Med 1990;323: 1289–98.

[17] Ballantyne CM, Raichlen JS, Nicholls SJ, et al. Effect of rosuvastatin therapy on coronary artery stenoses assessed by quantitative coronary angiography: a study to evaluate the effect of rosuvastatin on intravascular ultrasound-derived coronary atheroma burden. Circulation 2008;117:2458–66.

[18] Dahlen GH. Incidence of Lp(a) among populations. In: Scanu AM, editor. Lipoprotein(a). New York: Academic Press; 1990. p. 151–73.

[19] Nielsen LB. Atherogenecity of lipoprotein(a) and oxidized low density lipoprotein: insight from in vivo studies of arterial wall influx, degradation and efflux. Atherosclerosis 1999;143:229–43.

[20] Maher VG, Brown B, Marcovina SM, Hillger LA, Zhao X, Albers JJ. Effects of lowering elevated LDL cholesterol on the cardiovascular risk of lipoprotein(a). J Am Med Assoc 1995;274:1771–4.

[21] Jaeger BR, Richter Y, Nagel D, et al. Longitudinal cohort study on the effectiveness of lipid apheresis treatment to reduce high lipoprotein(a) levels and prevent major adverse coronary events. Nat Clin Pract Cardiovasc Med 2009;6:229–39.

[22] Keller C. Apheresis in coronary heart disease with elevated Lp(a): a review of Lp(a) as a risk factor and its management. Ther Apher Dial 2007;11:2–8.

[23] Borberg H. Comparison of different Lp(a) elimination techniques: a retrospective evaluation. Transfus Apher Sci 2009;41:61–5.

[24] Bambauer R, Schiel R, Latza R. Low density lipoprotein apheresis in treatment of hyperlipidemia: experience with four different technologies. Ther Apher 2000;4:213–7.